## REMARKS

Applicants have amended claim 1 by deleting the rejected phrase "optionally derivatized" from the claims even though it is believed that this term would be understood by one of ordinary skill in the art and does not render the claims indefinite in an effort to expedite the prosecution of this application to an early allowance. In addition, claim 1 was further amended to point out that the antigens selected from the group consisting of ~~optionally derivatized~~ explosives and narcotics synthetically bound via amide-group-formation to the SAM-forming OEG molecule, see page 3, lines 28-30, i.e. "The low molecular weight antigens are synthetically bound to the OEG molecules prior to SAM formation by reacting functional groups on the antigens with functional groups terminating the OEG thiol."

As previously amended, claim 1 has been clarified by inserting a) and b) in front of the two components forming the mixed SAM. The difference between these components is that in a) there is only (OEG) -terminated amide group-containing alkyl thiols and in b) there is (OEG) -terminated amide group-containing alkyl thiols coupled to antigens via amide-group formation. Both a) and b) are firmly attached to the metal surface via their respective thiol-end. Both in a) and b) the alkyl portion of the molecule has 1 -20 methylene groups and the OEG portion of the molecule has 1-15 ethylene oxy units. The antigens in b) are reversibly bound to antibodies. (These antibodies will be displaced in case their antigens are present in a test solution). New claims 13 and 14 have been added to further specify this aspect of the invention as fully supported by the specification as originally filed, see for example page 7 and figure 7.

The last paragraph of the present specification, page 3, explains that the low molecular weight antigens are synthetically bound to the OEG molecules prior to SAM formation by reacting functional groups on the antigens with functional groups terminating the OEG alkyl thiol. On page 7, lines 7-10 is described: A mixed monolayer was produced that contained two kinds of molecules, the first being protein repellent and the second being a TNT-analogue, thereby making it possible to obtain SAMs containing a varying amount of analogue that displays low levels of non-specific binding. Applicants most respectfully submit that all the claims now present in the

application are in full compliance with 35 U.S.C. 112 and are clearly patentable over the references of record.

The rejections under 35 USC 112, first and second paragraphs have been obviated by the amendments to the claims. Accordingly, it is most respectfully requested that these rejections be withdrawn.

The rejection of claims 1, 2, 6 and 7 under 35 U.S.C. 103(a) as being unpatentable over Willner et al. in view of Svedhem et al. and Bentley has been carefully considered but is most respectfully traversed in view of the amendments to the claims, the comments already of record and the following comments.

As previously noted, the Willner reference discloses the formation of cystamine monolayer on a gold electrode (page 23, lines 14-24 and Fig. 4). As is evident from Fig. 4, the monolayer is first formed and thereafter the antigen is added so that an antigen-cystamine monolayer immobolized on the electrode is obtained (page 4, lines 2-3). In this Willner reference, there is no suggestion of any other "capturing agent" than cystamine, only a very non-specific mentioning of a sulfur containing moiety as the capturing agents is mentioned on page 14, lines 22-23. There is no discussion of any possible effects of the "capturing agent" in the Willner reference, and therefore there is no motivation for one of ordinary skill in the art to modify said "capturing agent". Moreover, it is recognized in the Official Action that Willner fails to teach a coated metal surface further comprising a self-assembled monolayer of oligo(ethylene-glycol)-terminated alkanethiol amides.

Applicants again wish to note that the coating of the present invention of a mixed self-assembled monolayer of only two distinct molecules, namely a)OEG-terminated amide group containing alkyl thiols and b)OEG-terminated amide group containing alkyl thiols containing antigens synthetically bound via amide group formation to the OEG molecule. These two molecules are the ones that participate in the SAM forming.

The Svedhem et al reference produces self-assembled monolayers (SAMs) of OEG molecules, some of which are terminated with a functional group, namely carboxylic acid. To the already formed SAM is coupled ligands, but as is well-known for a man of ordinary skill in the art, there are no 100% chemical reactions, so there will be at least three types of molecules in the coating of the Svedhem et al reference, namely

OEG, OEG terminated with carboxylic acid and OEG terminated with amide coupled ligands. In practice, there will very likely be a number of different products formed if one attempts to attach an antigen to an already created SAM surface. By activating the carboxylic acid group as disclosed by Svedhem et al one would get, in addition to hydrolysis, various cross-reactions between the carboxylic groups; crosslinking between the different antigens etc. So, one would not get a controlled surface. If, as in the current invention, the carboxylic group is derivatized *prior to* attachment to the surface, it is possible to purify the OEG-antigen molecule *prior to* the creation of the SAM, which will guarantee that there will be a reproducible surface coating composed of only two types of well defined molecules.

From a product quality point of view, it is desirable to have only two types of molecules in the SAM, as is disclosed in the current specification and claims.

Further, in the Svedhem et al reference there is no disclosure of any antibodies reversibly bound to the ligands attached to the SAMs.

Applicants are not aware of any prior art where an antigen has been coupled to a SAM forming molecule prior to formation of the SAM. Therefore, it is not obvious to a man of ordinary skill in the art that it would be possible to do so, and of course, the resulting product could not either be obvious.

Applicants have previously noted, Svedhem et al, however, produce SAMs with planar biosensing interfaces for possible subsequent interaction with large entities such as phages or cells. (see page 4494, right column, lines 5 and last sentence of the first passage).

Thus, the Svedhem references does neither discloses nor suggests a mixed SAM of two different molecules, one of which contains an antigen and a reversibly bound antibody ready for displacement reactions with analyte antigens in accordance with the presently claimed invention. In the Official Action it is urged that OEG-terminated alkanethiol amides can be used as spacer molecules but this is clearly in the same molecule and not in two different molecules as in the presently claimed invention. There is no suggestion of this in any of the references relied upon in the rejection. Further, there is no indication of success in forming SAM monolayers of non-identical starting compounds. The teaching of this reference does not overcome the deficiencies

of the primary reference.

The Svedham reference describes two step procedures for obtaining a SAM with biologically active molecules. First a SAM is produced and then an amine derivative is surface coupled to carboxylate SAMs (see page 4495, left column, lines 6,7). On the same page, right column lines 12 -15, there is the disclosure that "A carboxylic acid group terminated analogue (6) has been included with which functionality for coupling of biomolecules of interest can be introduced into the monolayer[17]." Applicants previously submitted an abstract of reference 17 found at www.pubmed.gov (J. Lahiri, et al., "A strategy for the generation of surfaces presenting ligands of studies of binding based on an active ester as a common reactive intermediate: a surface plasm on resonance", Anal Chem, Feb. 15, 1999, vol. 71, no. 4), which describes the preparation of a mixed SAM of molecules of different lengths, wherein one type of molecule terminated with -OH and the other type of molecule is terminated with $-OCH_2COOH$. Then reactive N-hydroxylsuccinimidyl ester were created from the carboxylic acid end groups and finally these were coupled to amines on a protein or ligand on the pre-formed SAM surface.

The Svedhem reference does not comprise any disclosure or suggestion of producing a SAM from two types of molecules, where one type of molecule is already coupled to a bioactive group as in the present invention. Please note that the amended claim 1 states that the coating consists of the molecules a) and b). Thus the coating does not comprise unreacted reactive groups but rather an "inert molecule" and a "biologically active molecule" only. This is in contrast to the disclosures in the Svedhem reference and reference 17 cited therein since chemical reactions do not produce only the desired coupling of two molecules in a solution with reactants. Some of the activated (e.g. N-hydroxylsuccinimidyl activated carboxylic acid endgroups) will be hydrolyzed or react in an unwanted direction) and there will always be an excess of one or the other reaction components. Therefore, the prior art will inevitably have activated carboxylic groups that will be hydrolyzed in the final product since there is no possibility to fully control attachment of the proteins or ligands to all activated carboxylic groups. From product control point of view, the present invention provides well defined mixed SAMs comprising a known amount of attached biomolecules whereas the prior art

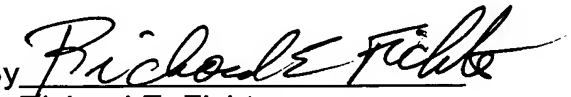
produces less well defined mixed SAMs comprising at best an approximately known amount of attached biomolecules. The teachings of the Bentley reference does not overcome the deficiencies of the primary references for reason previously of record.

In summary, most prior art is concerned with planar surfaces of SAMs, which may be of mixed SAMs, but the SAMs already exist when they are used for binding bioactive ligands to the surfaces. In the present invention, the bioactive molecule is coupled to one of two SAM-forming molecules prior to the formation of a SAM. The products of the invention are therefore not contaminated by non-reacted reactive groups and hydrolyzed products. The cited Willner et al reference does not disclose SAMs, nor does Bentley et al. Accordingly, it is most respectfully requested that this rejection be withdrawn.

The rejection of claims 3-5 under 35 U.S.C. 103(a) as being unpatentable over Willner in view of Svedham and Bentley as applied to claim 1 above and further in view of Duffy has been carefully considered but is most respectfully traversed in view of the above comments and those already of record. While Applicants appreciate that Duffy discloses arrays or patches for biomolecule binding, this reference does not disclose displacement reactions nor the formation of mixed molecules in the SAM. Accordingly, it does not overcome the deficiencies of the primary references and therefore it is most respectfully requested that this rejection be withdrawn.

In view of the above comments and further amendments to the claims, favorable reconsideration and allowance of all the claims now present in the application are most respectfully requested.

Respectfully submitted,
BACON & THOMAS, PLLC

By 
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